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(54) Title: METHODS AND MEANS FOR TREATING PROTEIN CONFORMATIONAL DISORDERS

(57) Abstract: This invention relates to the recognition that autophagy plays a key role in the clearance of the intracellular protein aggregates which characterise Protein Conformational Disorders, such as Huntington's disease and Parkinson's disease. Methods and uses of autophagy inducing agents, such as rapamycin macrolides, in the treatment of Protein Conformational Disorders, are described herein.

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AMENDED CLAIMS

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30. Use according any one of claims 17 to 23 wherein the disorder is a prion disorder.

31. Use according to claim 30 wherein the prion disorder is CJD.

32. A method of identifying an agent useful in the treatment of a protein conformational disorder comprising;

contacting a mammalian cell with a test compound; and,

determining the autophagy activity of said cell,

an increase in autophagy activity in the presence of said compound being indicative that the compound is a candidate agent for use in the treatment of a protein conformational disorder.

33. A method according to claim 32 wherein the cell comprises a heterologous nucleic acid encoding an aggregation-prone polypeptide.

34. A method according to claim 33 wherein said heterologous nucleic acid is operably linked to an inducible promoter.

35. A method according to claim 33 or claim 34 comprising expressing said nucleic acid and stopping said expression, prior to contacting the mammalian cell with the test compound.

36. A method according to any one of claims 32 to 35 comprising modifying the compound to optimise the pharmaceutical properties thereof

37. A method according to any one of claims 32 to 36 comprising formulating the test compound into a pharmaceutical composition.

38. A method of producing an agent for the treatment of a protein conformational disorder comprising;

modifying rapamycin to produce a rapamycin derivative; and; determining the autophagy inducing activity of said derivative.

39. A method according to claim 38 comprising determining the ability of said derivative to inhibit mTOR.

40. A method according to claim 38 or claim 39 comprising determining the ability of said derivative to enhance the clearance of cytoplasmic protein aggregates.